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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,913	08/30/2000	Shigeki Ono	0018-1093-0	3100

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/446,913	Applicant(s) ONO ET AL.	
	Examiner Anne Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The responses filed January 9, 2002 (Paper No. 7) and April 25, 2002 (Paper No. 9) have been entered. The Sequence Listing filed January 9, 2002 (Paper No. 7) has been entered. The amendment to the specification has been entered as requested.

Claims 1-4 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The claims are directed to a brain-protective agent comprising an NF-κB decoy. However, no particular structural limitations are recited for the agent. Thus, the claims are broadly directed to any compound that functions in the manner intended, i.e. in protecting the brain through some type of interaction with NF-κB. All claims recite an intended use, i.e. that the agent can be used for brain protection.

However, the specification does not provide a written description of any substance that can be used for brain protection other than SEQ ID NO: 1. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only SEQ ID NO: 1 is disclosed as

an agent that acts as an NF-κB decoy and provides protection against particular types of brain damage when delivered using a cationic liposomal delivery system. SEQ ID NO: 1 is described as a rabbit NF-κB recognition sequence. The specification does not describe other targets for other species. Moreover, no other brain-protective agents of the type claimed are described. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, the specification does not describe any other brain-protective agents by other relevant identifying characteristics.

A nucleic acid molecule is a complex chemical compound, and it is well-established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials. See *Oka* 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinquish it. **It is not sufficient to define it solely by its principal biological property**, because an alleged conception having no more specificity than that **is simply a wish to know the identity of any material with that biological property**. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the genus of brain-protective agents claimed, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus of NF-κB decoys that can be used as brain-protective agents.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a brain-protective agent comprising SEQ ID NO: 1 and a liposomal delivery system, wherein the agent diminishes cerebral vasospasm associated with subarachnoid hemorrhage, does not reasonably provide enablement for any brain-protective agent comprising an NF-κB decoy. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a brain-protective agent. The specification discloses the administration of a double-stranded oligonucleotide (SEQ ID NO: 1) using a cationic liposomal delivery system. The only use taught in the specification for the claimed compositions is for producing a therapeutic effect, specifically brain protection. Thus, the invention is directed to administering a nucleic acid molecule for therapy. Therefore, the only use for the claimed compositions is for gene therapy. The claims are very broad with regard to the intended patients and disorders that can be treated. The claims encompass an intended use for treating any type of brain disorder. When an intended use is recited, the claimed composition must be enabled for the full scope of the intended use. The specification contemplates a wide variety of brain disorders that allegedly could be treated using the claimed compositions (see page 3, paragraph 3 to page 4, paragraph 1). However, the specification does not teach how to use the claimed compositions over the full scope, for the following reasons.

Gene therapy is not routinely successful. Therefore, the disclosure must teach how to use the claimed compositions for the intended use, over the full scope. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder

Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods for *in vivo* gene therapy. Thus, absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect in an immunocompetent animal, such as a human, the claims directed to gene therapy are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for targeting appropriate cells for the treatment of the diseases referred to in the specification. The specification contemplates treating a wide variety of diseases and disorders using the claimed compositions, including cerbral vasospasm following subarachnoid hemorrhage, cerebral infarcts in cerebral thrombosis and cerebral embolism, sequelae of intracranial hemorrhage, cerebrovascular dementia, hydrocephalus, cerebral arterial anomaly-angioma, various brain tumors, Parkinson's syndrome, cerebral arteriosclerosis, meningitis, encephalitis, AIDS, various types of encephalopathy, multiple sclerosis, and brain disorders arising from neuronal death caused by serious head trauma (see pages 3-4). Only general guidance is offered with regard to delivering the agent to the appropriate site. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. More importantly, the disclosure does not offer a solution to this problem. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that "for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of

cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain et al. review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the quantity of experimentation necessary to determine appropriate parameters for using the claimed compositions for their intended use, and given the lack of applicable working examples demonstrating an *in vivo* effect for brain disorders other than cerebral vasospasm associated with subarachnoid hemorrhage, the limited guidance in the specification, particularly with regard to the nucleic acid that is to be delivered, the broad scope of the claims, and the unpredictability for using the claimed compositions in treating the wide variety of disorders set forth in the specification, undue experimentation would have been required for one skilled in the art to make and use the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are indefinite in their recitation of "an NF-κB decoy" because it is unclear what would constitute "an NF-κB decoy." The specification indicates on page 3 that an NF-κB decoy is a compound that specifically competes with the nucleic acids to which NF-κB binds. However, this definition is non-limiting. Thus, the metes and bounds are not clearly set forth.

Claims 2-4 are indefinite in their recitation of "the brain disorder arising from encephalopathy" because there is no antecedent basis for "the brain disorder."

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER